Editorial

Suicide: a neurobiological point of view

Suicídio: um ponto de vista neurobiológico

Despite the prominence of suicide as a leading cause of death throughout most countries of the world and the substantial evidence supporting the role of biological factors in suicide predisposition and risk mediation/moderation, its biological basis remains poorly understood and inadequately studied. While several psychosocial factors associated with suicide have been described in detail, numerous studies have also documented an inherited basis for suicidal behaviour, suggesting that the discovery of such genetic factors could lead, in the long run, to some improvements in prevention. The etiology of suicidal behaviour is likely to overlap with that of other psychiatric disorders, owing to the high rates of mood disorders and other psychiatric diagnoses amongst victims of suicide. However, numerous studies controlling for the presence of psychiatric conditions have indicated that the liability for suicide is independent from (but conditional on) the genetic factors mediating susceptibility for major psychiatric disorders. Impulsive-aggressive behaviors also play a critical role in suicide predisposition. Perspectives on the neurobiological basis of suicide have begun to converge in recent years on several key areas, which will be elaborated on below.

The primary biological focus in studies of suicide has been oriented upon the serotonin system, following the observation of an inverse correlation between CSF 5-HIAA levels and suicide risk in depression,[1] as well as the finding of an increased density of serotonin binding sites in the frontal cortex of suicide victims. These observations, combined with reports of a blunted prolactin response to challenge with D-fenfluramine in suicide attempters, as well as fewer presynaptic serotonin transporter sites and upregulated levels of the 5-HT1A receptor in ventromedial prefrontal cortex of suicide completers collectively imply a role for both serotonin and this brain region in suicide. However, multiple systems appear to play a role in regulating the risk of suicide, and under this perspective, recent findings pointing to the possible implication of protein kinase A and C in the suicide neurobiology are encouraging.[2] Another interesting lead that, in spite of much controversy, is supported by several lines of evidence concerns the relationship between low cholesterol levels and suicidal behaviour. This is an intriguing association with unclear candidate mediating mechanisms to explain how serum cholesterol levels may have an effect on behaviour. In any case, the investigation of components of the lipid metabolisms in the neurobiology of suicide and related behaviours has gained renewed interest in light of the growing evidence demonstrating essential roles for cholesterol in brain synaptogenesis, as well as evidence suggesting that alterations in brain sterol composition may mediate this association.[3]

Direct examination of genes controlling serotonergic neurotransmission has occasionally demonstrated replicated association between sequence variants and suicidality, primarily for the serotonin transporter. However, the absence of consistent evidence for association of specific genetic polymorphisms with phenotype is not unique to the study of suicide, but also underlies research in most complex phenotypes. One of the most important confounding factors in

these types of studies is genetic heterogeneity, whereby multiple genetic variants can produce the same visible phenotype, as well as phenotypic heterogeneity or diverse phenotypic subtypes under the same clinical presentation. In the face of a multifactorial and polygenic mode of disease transmission, the power of traditional case/control association studies is significantly diminished unless a narrow definition of the phenotype can be employed. With the abundant interactions likely to exist between developmental, psychosocial, and genetically inherited risk factors for suicide,[4] a problematic situation arises which can perhaps be ameliorated somewhat through better phenotyping. However, it will also be necessary to utilize increasingly more powerful, sensitive, and robust approaches to isolate the genetic contribution to this complex behaviour in future investigations.

One methodology that has become increasingly utilized in the study of complex disorders is microarray analysis of gene expression. Avoiding the pitfalls inherent in treating behaviours as simple Mendelian traits, this type of microarray allows for the simultaneous assessment of tens of thousands of expressed sequences, and as such is capable of identifying patterns of gene expression between different groups or changes in expression of specific candidate sequences, but also requires that meticulous attention be paid to the parameters associated with data processing and that appropriate analytic methods be carried out upon vast amounts of data within the context of the biological problem. The wide-scale implementation of microarray technology in studies of psychiatric conditions and behaviours has only just begun, but shows promise particularly with regards to discovery of as yet unknown aspects of suicide neurobiology.[5] As these types of studies become more commonplace, a better picture of the genes involved in the pathophysiology of suicidal behaviours will emerge, directing more focused investigations into particular pathways and genes.

In tandem with the surveillance of levels of gene expression, massively parallel technologies capable of typing thousands of sequence variations within biological samples are becoming standardized in the form of single nucleotide polymorphism (SNP) genotyping chips. Of further benefit, these data will provide more powerful methods for detecting the interactions between multiple genetic loci that are likely to exist in a suicidal behaviour phenotype. While a formidable challenge is posed in the search for the neurobiological correlates of suicide, progressive research strategies are now enabling us to both understand and move beyond some of the more customary domains of study, eventually rendering suicide risk assessment a less subjective practice and allowing for the development of more effective treatment intervention strategies for susceptible individuals.

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